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Contribution of catechol-*O*-methyltransferase Val158Met polymorphism to endometrial cancer risk in postmenopausal women: a meta-analysis

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ABSTRACT. Catechol-*O*-methyltransferase (COMT) is a critical enzyme to detoxify the carcinogenic catechol estrogen and the Val158Met polymorphism of COMT could influence its enzymatic activity. Recent epidemiological studies have investigated the correlation of COMT Val158Met polymorphism with endometrial cancer risk; however, the results are inconsistent. To better evaluate the role of COMT Val158Met in endometrial carcinogenesis, we performed this meta-analysis, considering menopausal status, study quality, ethnicity, and source of controls. Eight eligible studies

including 5109 subjects were collected from PubMed, CNKI, and Chinese Biomedicine Database (updated until September 21, 2012). Although no obvious associations were detected between COMT Val158Met and endometrial cancer susceptibility in the pooled analysis, we noted significantly decreased endometrial cancer risk for Val/Met versus Val/Val, and Met/Met + Val/Met versus Val/Val genetic models in the postmenopausal female (OR = 0.795, 95%CI = 0.656-0.962, P = 0.019; and OR = 0.819, 95%CI = 0.683-0.983, P = 0.032; respectively), and similar results existed in high-quality studies (OR = 0.835, 95%CI = 0.726-0.961, P = 0.012; and OR = 0.853, 95%CI = 0.747-0.974, P = 0.019; respectively). However, no evidence of association was noted in different ethnic groups and sources of controls. In conclusion, our results suggested that the COMT Val/Val genotype might act as a potential endometrial cancer risk factor in postmenopausal women. Further studies are needed to investigate the interactions between COMT Val158Met polymorphism and endometrial cancer in a specific population.

Key words: COMT; Polymorphism; Endometrial cancer; Meta-analysis

INTRODUCTION

Endometrial cancer is a gynecological malignancy prevalent worldwide and the death rate attributed to it has increased in recent years (Sorosky, 2008). Various risk factors are involved in the development of endometrial cancer, such as prior exogenous estrogen administration, obesity, nulliparity, diabetes, genetic factors, etc. (Sorosky, 2008). Estrogen biosynthesis and metabolism are closely associated with tumorigenesis, and the functional gene polymorphisms regulating these processes can influence the levels of estrogen and intermediate products, which may potentially contribute to the differences in individual susceptibility to endometrial cancer (Huber et al., 2002).

Three major estrogens exist *in vivo*: estrone (E1), estradiol (E2), and estriol (E3). These estrogens can be hydroxylated into 2-hydroxy- and 4-hydroxy-estrone/estradiol (2/4-OH catechol estrogens) (Zhu and Conney, 1998a), and then, the 2/4-OH catechol estrogens are inactivated by methylation to form 2/4-methoxy-estrone/estradiol (2/4-MeO-E1/E2). The methylation modification is catalyzed via catechol-O-methyltransferase (COMT) (Ball et al., 1972). If the methylation reaction is incomplete, these catechol estrogens will be oxidized to semiquinones and quinines; this process can produce reactive oxygen species, causing DNA damage and tumor initiation (Cavalieri et al., 1997). Therefore, COMT plays the critical role of detoxifying carcinogenic catechol estrogens. Moreover, the 2-methoxy-estradiol (2-MeO-E2) metabolite catalyzed by COMT can inhibit the proliferation and migration of endothelial cells, angiogenesis and cytotoxin, and can induce apoptosis to suppress carcinogenesis (Zhu and Conney, 1998b). A functional polymorphism exists in COMT gene, the G→A transition at codon158 (rs4680) in exon 4, leading to the substitution of valine to methionine (known as Val158Met). The homozygous mutant Met/Met genotype has been reported to decrease the COMT methylation

activity by 3~4 folds compared with wild-type Val/Val genotype; the heterozygous Val/Met genotype has intermediate activity (Dawling et al., 2001). Since COMT Val158Met polymorphism can influence the enzymatic activity and may further alter the accumulation of circulating levels of carcinogenic catechol estrogens, therefore, Val158Met has long been the focus of hormone-related cancers such as prostate (Suzuki et al., 2007), breast (He et al., 2012), and endometrial cancer.

In recent years, many studies have investigated the relationship between COMT Val158Met polymorphism and endometrial cancer susceptibility (McGrath et al., 2004; Zimarina et al., 2004; Doherty et al., 2005; Tao et al., 2006; Liu et al., 2007; Szyllo et al., 2007; Zhao et al., 2007; Hirata et al., 2008a,b; Li et al., 2010); however, the results are controversial. Zhao et al. (2007) found that COMT Val/Val carriers may have decreased endometrial cancer risk versus individuals with Met/Met genotype, whereas Doherty et al. (2005) demonstrated that COMT Val/Met and Met/Met carriers may show only a slight reduction in the risk. In contrast, others have not found any correlation (McGrath et al., 2004; Zimarina et al., 2004; Tao et al., 2006; Liu et al., 2007; Szyllo et al., 2007; Hirata et al., 2008a,b; Li et al., 2010). The inconsistent conclusions may be due to a possible minor effect of the polymorphism on endometrial cancer or the small sample size in single studies with inadequate statistical power of complex traits. Meta-analysis is a powerful statistical tool pooling different studies to overcome deficiencies such as small sample size, which will provide more reliable results. So far, no meta-analysis has assessed the association between COMT Val158Met polymorphism and endometrial cancer risk. Here, we performed a meta-analysis of eight eligible studies, including 2296 cases and 2813 controls, to evaluate the correlation more precisely.

MATERIAL AND METHODS

Publication search

To identify all studies that investigated the association between COMT Val158Met polymorphism and endometrial cancer risk, we conducted a literature search in PubMed, CNKI (Chinese National Knowledge Infrastructure), and Chinese Bio-medicine Database by using following terms: “catechol-*O*-methyltransferase”, “COMT”, “polymorphism”, “endometrial cancer”, as well as their combinations. References cited in the retrieved and review articles were also searched manually. There were no language restrictions to the publications and the last update was dated September 21, 2012.

Inclusion and exclusion criteria

Eligible studies were selected on the basis of the following criteria: (a) full-text articles about COMT Val158Met polymorphism and endometrial cancer risk; (b) case-control studies with available data for estimating the odds ratio (OR) with 95% confidence interval (CI); and (c) if the studies used overlapping case-control data, only the recent and most complete studies were included in our meta-analysis. The main exclusion criteria were (a) not case-control studies, (b) control population including patients with tumors, and (c) duplication of a previous publication.

Data extraction

Two investigators (G. Lin and J. Zhao) independently extracted information from all eligible publications to reduce bias in data collection. The data comprised the first author's surname, year published, country of origin, ethnicity, sample source, specimens of cases, sample size, and methods for detecting COMT Val158Met genotypes, total number of cases and controls, numbers of cases and controls with Val/Val, Val/Met, and Met/Met genotypes, respectively.

Quality score assessment

The quality of these studies was also evaluated independently by the same two investigators according to the predefined quality assessment rules in Table 1. The scores were determined using both traditional epidemiological consideration and cancer genetic issues (Jiang et al., 2010). Checking and discussion between the two investigators led to consensus on all the items. The total score ranged from 0 (worst) to 15 (best). Papers scoring <10 were classified as "low quality" and those scoring ≥10 as "high quality."

Table 1. Scale for quality assessment.

Criteria	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens of cases determining genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
≥1000	3
≥500 but <1000	2
≥200 but <500	1
>0 but <200	0

Statistical analysis

For each study, Hardy-Weinberg equilibrium (HWE) was analyzed with the Chi square-based test. The strength of the association between COMT Val158Met polymorphism and endometrial cancer risk was assessed by OR corresponding to 95%CI according to the method described by Woolf (1955). Heterogeneity among studies was detected by Cochran's Chi square-based Q test (Higgins et al., 2003). If the result of heterogeneity test had a P value of <0.1, the random effect model using the DerSimonian and Laird method was employed to pool the results, which yielded wider CIs (DerSimonian and Laird, 1986). Otherwise, the fixed-effect model using the Mantel-Haenszel method was performed (Mantel and Haenszel,

1959).

The significance of the pooled ORs was determined via the Z-test ($P < 0.05$ suggests significant association). Subgroup analysis was stratified by menopausal states (premenopausal and postmenopausal), study quality ("high" and "low"), ethnicity (Caucasian, Asian, and Mixed), and control sources (population-based and hospital-based). One-way sensitivity analyses were used to evaluate the stability of the results obtained. Publication bias was tested by both the Begg funnel plot (Begg and Mazumdar, 1994) and the Egger's linear regression test (Egger et al., 1997). If the funnel plot was asymmetric and the Egger test gave a P value of <0.05, publication bias was assumed to exist (Egger et al., 1997). Then, the Duval and Tweedie non-parametric "trim and fill" methods were performed to adjust for it. All statistical tests were carried out with the Stata software version 10.0 (Stata Corporation, College Station, TX, USA) in this study.

RESULTS

Study characteristics

We identified 205 papers investigating the relationship between COMT polymorphisms and cancers from PubMed database (190) and from Chinese publications (15) as shown in Figure 1. After reviewing the titles and abstracts, 60 papers discussing COMT Val158Met polymorphism were selected, of which 14 studied endometrial cancer. When extracting data from the 14 candidate papers, five papers were excluded because four articles lacked case-control data and the population in one paper (Hirata et al., 2008b) overlapped with another included study (Hirata et al., 2008a). Thus, nine case-control studies met our inclusion criteria (McGrath et al., 2004; Zimarina et al., 2004; Doherty et al., 2005; Tao et al., 2006; Liu et al., 2007; Szyllo et al., 2007; Zhao et al., 2007; Hirata et al., 2008a; Li et al., 2010), which were composed of five papers in English (McGrath et al., 2004; Zimarina et al., 2004; Doherty et al., 2005; Tao et al., 2006; Hirata et al., 2008a), three in Chinese (Liu et al., 2007; Zhao et al., 2007; Li et al., 2010), and one in Polish (Szyllo et al., 2007) independently translated by a research assistant.

The main characteristics of these studies are listed in Table 2. In the nine studies, four studies involved Caucasians (McGrath et al., 2004; Zimarina et al., 2004; Szyllo et al., 2007; Hirata et al., 2008a), four involved Asians (Tao et al., 2006; Liu et al., 2007; Zhao et al., 2007; Li et al., 2010), and the other one involved Caucasian and African populations (Doherty et al., 2005). As for sample sources, three papers were population-based (Doherty et al., 2005; Tao et al., 2006; Hirata et al., 2008a) and six were hospital-based (McGrath et al., 2004; Zimarina et al., 2004; Liu et al., 2007; Szyllo et al., 2007; Zhao et al., 2007; Li et al., 2010). The sample sizes ranged from 164 to 2057 subjects. The genotype distributions of the COMT Val158Met in endometrial cancer cases and controls are shown in Table 3. Moreover, two studies provided detailed data of the premenopausal and postmenopausal subpopulations (McGrath et al., 2004; Tao et al., 2006), and one study discussed postmenopausal detection (Szyllo et al., 2007). The genotype frequencies of the controls from eight studies were in agreement with Hardy-Weinberg equilibrium (HWE), the one study (Liu et al., 2007) deviating from HWE was excluded in the final meta-analysis as indicated in Figure 1. Then, according to the predefined quality score rules in

Table 1, five studies (McGrath et al., 2004; Zimarina et al., 2004; Doherty et al., 2005; Tao et al., 2006; Li et al., 2010) with >200 subjects, using blood for genotyping, and with a quality score of >10 were classified as high quality, whereas the other three (Szyllo et al., 2007; Zhao et al., 2007; Hirata et al., 2008a) with relative small sample size, using tissue DNA for genotyping, and deviating from HWE in controls with a score of <10 were labeled as low quality. Ultimately, eight eligible studies with 2296 endometrial cancer cases and 2813 controls were collected to perform meta-analysis in this study.

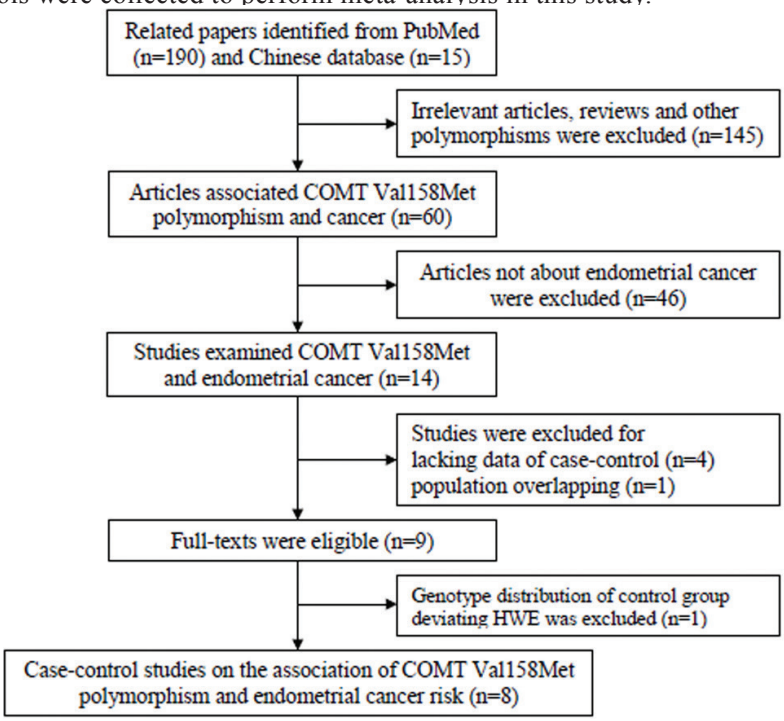

Figure 1. Flow chart of study selection explaining the eight eligible case-control studies included in the meta-analysis.

Table 2. Main characteristics of studies included in this meta-analysis.

First author reference	Year	Country	Ethnicity	Sample source (cases/controls)	Specimens of cases	Sample size (cases/controls)	Genotyping method	Quality score
Hirata	2008a	USA	Caucasians	Hospital/population	Tissue	150/165	PCR-RFLP and DNA sequencing	<10
Szyllo	2007	Polish	Caucasians	Hospital/hospital	Tissue	151/197	PCR-RFLP	<10
Zhao	2007	China	Asian	Hospital/hospital	Tissue and blood	132/110	PCR-RFLP	<10
Tao	2006	China	Asian	Population/population	Blood and exfoliated buccal cells	1031/1026	Taqman	>10
Doherty	2005	USA	Caucasian and African	Population/population	Blood	371/420	PCR-RFLP	>10
Zimarina	2004	Russia and Norway	Caucasians	Hospital/hospital	Blood	124/140	PCR-RFLP	>10
McGrath	2004	USA	Caucasians	Hospital/hospital	Blood	215/641	PCR-RFLP	>10
Liu	2007	China	Asian	Hospital/hospital	Tissue	80/84	PCR-RFLP	<10
Li	2010	China	Asian	Hospital/hospital	Blood	122/114	PCR-RFLP	>10

Table 3. Genotype distribution of COMT Val158Met in the cases and controls (n%).

First author reference	Genotype						
	Cases			Controls			HWE
	Val/Val (N%)	Val/Met (N%)	Met/Met (N%)	Val/Val (N%)	Val/Met (N%)	Met/Met (N%)	Controls
Hirata	32 (21.3)	81 (54.0)	37 (24.7)	48 (29.1)	90 (54.5)	27 (16.4)	0.16
Szyllo	46 (30.5)	81 (53.6)	24 (15.9)	48 (24.4)	110 (55.8)	39 (19.8)	0.09
Zhao	39 (29.5)	77 (58.3)	16 (12.1)	52 (47.3)	50 (45.5)	8 (7.3)	0.39
Tao	563 (54.6)	383 (37.1)	85 (8.2)	534 (52.0)	425 (41.4)	67 (6.5)	0.15
Doherty	97 (26.1)	174 (46.9)	100 (27.0)	90 (21.4)	207 (49.3)	123 (29.3)	0.87
Zimarina	29 (23.4)	65 (52.4)	30 (24.2)	23 (16.4)	73 (52.1)	44 (31.4)	0.43
McGrath	55 (25.6)	105 (48.8)	55 (25.6)	161 (25.1)	308 (48.0)	172 (26.8)	0.33
LIU	42 (52.5)	33 (41.3)	5 (6.3)	35 (41.7)	46 (54.8)	3 (3.6)	0.01*
LI	90 (78.3)	26 (21.3)	6 (4.9)	71 (62.3)	35 (30.7)	8 (7.0)	0.22
Premenopausal							
Tao	229 (51.2)	176 (39.4)	42 (9.4)	204 (51.8)	160 (40.6)	30 (7.6)	0.86
McGrath	11 (20.4)	29 (53.7)	14 (25.9)	23 (24.5)	48 (51.1)	23 (24.5)	0.84
Postmenopausal							
Tao	334 (57.2)	207 (35.4)	43 (7.4)	330 (52.2)	265 (41.9)	37 (5.9)	0.09
McGrath	43 (27.4)	73 (46.5)	41 (26.1)	134 (25.1)	253 (47.5)	146 (27.4)	0.25
Szyllo	46 (30.5)	81 (53.6)	24 (15.9)	48 (24.4)	110 (55.8)	39 (19.8)	0.09

Val = Valine; Met = Methionine;*Deviation from HWE.

Meta-analysis results

The main results of this meta-analysis are listed in Table 4. No significant associations between COMT Val158Met polymorphism and endometrial cancer susceptibility were observed when the studies were pooled, in all the genetic models. However, in stratified analysis based on menopausal status and study quality, reduced risk of endometrial cancer were found in case of Val/Met versus Val/Val and Met/Met + Val/Met versus Val/Val comparisons for the postmenopausal subpopulation (Val/Met versus Val/Val: OR = 0.795, 95%CI = 0.656-0.962, P = 0.019; Met/Met + Val/Met versus Val/Val: OR = 0.819, 95%CI = 0.683-0.983, P = 0.032; as shown in Figure 2A and B), and similar results also existed in the five high-quality studies (Val/Met versus Val/Val: OR = 0.835, 95%CI = 0.726-0.961, P = 0.012; Met/Met + Val/Met versus Val/Val: OR = 0.853, 95%CI = 0.747-0.974, P = 0.019; as shown in Figure 2C and D). When subgroup analysis based on ethnicity and source of controls was performed, no evidence of associations was discovered among these subpopulations.

Sensitivity analyses

Influence analysis was performed to determine the effect of individual data on the pooled OR by omitting one study at a time when repeating the meta-analysis. Most of the corresponding pooled OR were not significantly altered (data not shown).

Publication bias

Both Begg's funnel plot and Egger's tests were employed to detect publication bias of the literature collected. Begg's funnel plots did not find any obvious asymmetry in any meta-analysis (figures not shown). Then, Egger's test was performed to gather statistical evidence of funnel plot symmetry, which still did not show any obvious publication bias in all genetic models studied, such as Val/Met versus Val/Val: Begg's test P = 0.902 and Egger test P =0.616; Met/Met + Val/Met versus Val/Val: Begg's test P = 0.902 and Egger test P = 0.798; Val/Val + Met/Met versus Val/Met: Begg's test P = 0.386 and Egger test P = 0.352. These analyses indicate that our results are statistically robust.

Table 4. Main findings of the meta-analysis for COMT Val158Met polymorphism and endometrial cancer risk.

Study groups	N	Sample size cases/controls	Val/Met *vs* Val/Val			Val/Met *vs* Met/Met			Met/Met + Val/Met *vs* Val/Val		
			OR (95%CI)	P	P_h	OR (95%CI)	P	P_h	OR (95%CI)	P	P_h
Total	8	2296/2813	0.926 (0.744-1.152)	0.492	0.035	0.937 (0.793-1.108)	0.447	0.45	0.935 (0.740-1.181)	0.573	0.151
Menopausal states											
premenopausal	2	501/488	1.006 (0.767-1.318)	0.968	0.58	0.840 (0.545-1.296)	0.431	0.63	1.045 (0.808-1.351)	0.738	0.743
postmenopausal	3	892/1362	**0.795 (0.656-0.962)**	**0.019**	0.822	0.919 (0.695-1.214)	0.551	0.26	0.819 (0.683-0.983)	0.032	0.351
Quality score											
<10	3	433/472	1.275 (0.723-2.246)	0.401	0.031	0.865 (0.596-1.254)	0.347	0.44	1.323 (0.706-2.480)	0.382	0.102
>10	5	1863/2341	0.835 (0.726-0.961)	0.012	0.612	0.956 (0.793-1.154)	0.346	0.64	0.853 (0.747-0.974)	0.019	0.298
Ethnicity											
Caucasian	4	640/1143	0.949 (0.745-1.209)	0.672	0.358	1.034 (0.807-1.326)	0.792	0.35	0.941 (0.748-1.183)	0.603	0.12
Asian	3	1285/1250	1.002 (0.554-1.809)	0.996	0.004	0.734 (0.537-1.005)	0.054	0.86	1.034 (0.572-1.867)	0.913	0.417
Mixed	1	371/420	0.780 (0.549-1.107)	0.165	-	1.034 (0.742-1.441)	0.844	-	0.770 (0.555-1.070)	0.12	-
Source of control											
population-based	3	1552/1611	0.872 (0.748-1.018)	0.083	0.227	0.830 (0.665-1.036)	0.1	0.22	0.949 (0.717-1.257)	0.715	0.093
hospital-based	5	744/1202	0.930 (0.624-1.386)	0.722	0.019	1.103 (0.853-1.428)	0.455	0.9	0.905 (0.594-1.379)	0.642	0.463

N = numbers of compared studies. Mixed, composed of Caucasian and African ethnic groups. P value of z-test for the association, $P < 0.05$ indicated the results were statistically significant and values were shown in bold. P_h value of *Q*-test for the heterogeneity, when $P_h < 0.1$, the random-effect model was used, otherwise the fixed-effect model was employed.

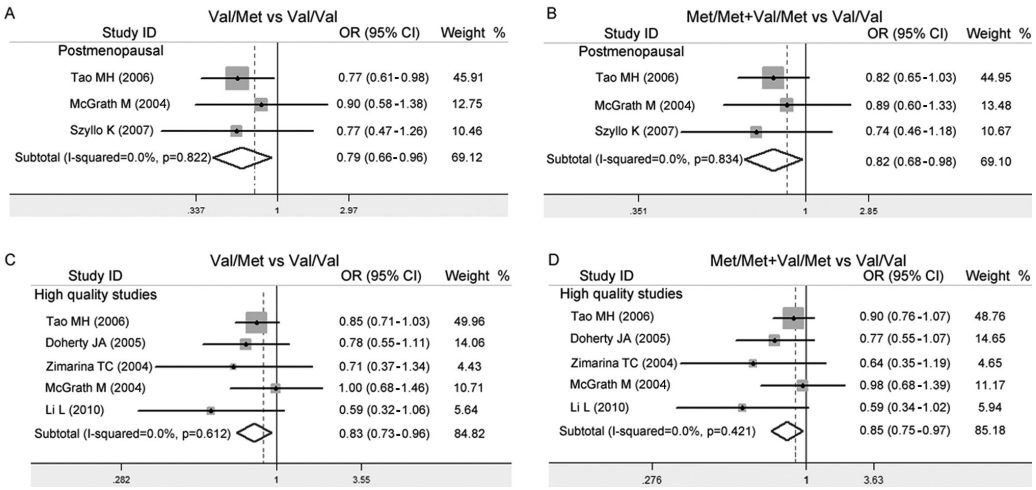

Figure 2. Forest plots of the association between COMT Val158Met polymorphism and endometrial cancer risk, for Val/Met versus Val/Val and Met/Met + Val/Met versus Val/Val genetic models via meta-analysis in the postmenopausal subgroup (**A** and **B**) and in the high-quality studies (**C** and **D**), respectively. The gray square centers and corresponding horizontal lines represent the study-specific OR and the accompanying 95%CI. The area of each square reflects its proportion to the sample size and the weight used in this analysis. All subtotal OR were calculated with fixed-effects models, and are presented by hollow diamonds.

DISCUSSION

Estrogens have long been thought to be involved in the pathogenesis of many diseases such as Alzheimer's syndrome, hypertension, breast cancer, endometrial cancer, etc. The following mechanisms may be involved. First, estradiol, the main member of estrogens, is a pleiotropic transcription factor involved in the activation of many disease-related genes with response elements (EREs) after binding to the estrogen receptor (ER) (Kushner et al., 2000). Second, the metabolites of estrogens have also closely been correlated with the development of various syndromes and cancers (Cavalieri et al., 1997). For instance, the accumulation of catechol estrogens may induce DNA damage and cause mutations in some pivotal genes. COMT is an important enzyme to inactivate carcinogenic catechol estrogens by methylation modification and to inhibit tumor initiation. *COMT* gene locates on the chromosome 22q11.2, contains six exons, and expresses in various mammalian tissues including the liver, kidney, endometrium, and breast, at high levels (Lundstrom et al., 1995). There are some single-nucleotide polymorphisms (SNPs) in the COMT gene, as summarized by the SNP500 Cancer Database (Packer et al., 2006): COMT SNPs in codon 72 of exon 3 (rs6267) and codon 102 of exon 4 (rs5031015) are very rare in Caucasians, whereas the SNPs in codon 62 (rs4633), 136 (rs4818), and 158 (rs4680) are common (http://snp500cancer.nci.nih.gov). As the polymorphism of the COMT codon 158 leads to Val-to-Met substitution, and the Met carriers may partially lose the methylation activity (Dawling et al., 2001), the COMT Val158Met has been extensively investigated for correlation with tumor risk, including in case of endometrial cancer. However, the results of recent studies are inconsistent for different races. One study involving women in South China found that the COMT Val/Val carriers may decrease the

endometrial cancer risk compared with the COMT Met/Met genotype (Zhao et al., 2007); another study involving Caucasian and African American populations showed that low-activity COMT Val/Met and Met/Met carriers have a slightly decreased risk (Doherty et al., 2005). Other studies involving American (McGrath et al., 2004; Hirata et al., 2008a), Polish (Szyllo et al., 2007), Chinese (Tao et al., 2006; Liu et al., 2007; Li et al., 2010), Russian, and Norwegian populations (Zimarina et al., 2004) did not observe significantly different distribution of the COMT Val158Met genotype in the endometrial cancer patients and controls.

To resolve the above issues stemming from COMT Val158Met polymorphism and endometrial cancer risk, we summarized these studies and performed meta-analysis for 2296 cases and 2813 controls to evaluate the overall effects. Our results indicate that Val158Met is not correlated with endometrial cancer susceptibility in pooled analysis, which suggest that the COMT Val158Met polymorphism alone may be insufficient to predict the risk, and the effects of other COMT regulatory variations, COMT haplotypes, and CpG hypermethylation of the COMT promoter should be considered. Moreover, women developing endometrial cancer often have high estradiol levels that can inhibit COMT expression (Xie et al., 1999) and may outweigh the activity difference resulting from Val158Met polymorphism. However, stratified analysis according to menopausal status, an important risk factor for endometrial cancer pathogenesis, showed that Val/Val plays obviously negative roles versus Val/Met ($P = 0.019$) and Met/Met + Val/Met ($P = 0.032$) in the postmenopausal women. This result is consistent with that of a previous study about COMT Val158Met on breast cancer risk (Thompson et al., 1998); they also found that COMT Val/Val genotype associated with increasing breast cancer risk in postmenopausal women. These data indicate the presence of complex interactions between COMT Val158Met and menopausal status in hormone-related cancers. In addition, the associations also existed among well-designed studies, Val/Val genotype may significantly increase endometrial cancer risk compared with Val/Met ($P = 0.012$) and Met/Met + Val/Met carriers ($P = 0.019$). Our classification of high-quality studies is helpful to minimize bias, enhance statistical power, and obtain plausible conclusions. However, we did not find evidence of the association between Val158Met and endometrial cancer in Asians, Caucasians, and mixed populations, suggesting that the genetic backgrounds of people belonging to different ethnicities and environments have little impact on the correlation. Although COMT Val158Met polymorphism may not act as an independent factor for predicting cancer risk, the correlation can be detected in some specific subpopulations such as in postmenopausal women.

Meanwhile, there are some limitations of this meta-analysis. First, the control sources were not uniform. Most hospital-based controls had endometrial diseases and some of them might have been at risk to develop cancer in future, although our results from both population- and hospital-based controls showed no difference. Second, we performed only unadjusted evaluation on the association, because some detailed data such as BMI (body mass index), estrogen administration, and smoking status were not available, and therefore, these potential interactions could not be further estimated. Third, meta-analysis is the retrospective research, which is subject to some methodological deficiencies. To minimize the bias, we followed the previous quality score system (Jiang et al., 2010) and classified five high-quality and three low-quality studies. Although the predefined quality assessment have considered the traditional epidemiological and oncological issues, and the scoring was performed independently by two investigators to reduce the subjective effects, more standard scoring procedures for such studies are still expected to be established in future.

In conclusion, our results suggest that COMT Val/Val carriers may significantly increase endometrial cancer risk in postmenopausal women, which may help us identify high-risk subpopulation and create more effective strategies for prevention and treatment. Further studies may be required to address the possible effects of different life styles and environmental factors on the association between COMT Val158Met polymorphism and endometrial cancer risk.

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